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MANUFACTURE OF CALCIUM GLUCONATE BY THE ELECTROLYTIC OXIDATION OF DEXTROSE[1]

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ABSTRACT

In a previous paper the authors[2] described a simple method for the preparation of the calcium salts of the aldonic acids by electrolytic oxidation of the aldose sugars in the presence of a bromide and calcium carbonate. This method has been applied on a larger scale and has proved to be very satisfactory for the manufacture of calcium gluconate in considerable quantity. The principal products of the reaction are calcium gluconate, carbon dioxide, and hydrogen. The calcium gluconate which crystallizes from the electrolyte is collected upon a filter, and the mother liquors containing the bromide are returned to the cell after the addition of more dextrose and calcium carbonate. Since the process is continuous, the raw materials and electrical energy are readily available and cheap, and the product is obtained without any expensive evaporation or difficult steps, it is now possible to prepare calcium gluconate at a very reasonable cost.

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I. INTRODUCTION

Among the many sugar derivatives which hold promise for future development and industrial application are the monobasic sugar acids which are obtained by mild oxidation of the aldose sugars. Although these compounds have been known for a long time and have been of great importance in acquiring our present knowledge of the molecular structures of the various sugars, until recently they have received little attention from those interested in applied chemistry. Gluconic acid in particular should find many uses because it may now be prepared at low cost. The calcium salt of the acid has already found some application in the medicinal field, while the free acid offers many possibilities for the future. The sugar acids and their salts resemble the sugars, in that they form soluble complex compounds with numerous substances. Hence they are able to hold in solution many difficultly soluble substances, as, for example, certain amphoteric hydroxides. The sugar acids are also unique in that they form two anhydrides or lactones.[3] One of these is formed by condensation of the carboxyl group in gluconic acid with the hydroxyl on the fourth, or gamma carbon, and the other by condensation with the hydroxyl on the fifth, or delta carbon. These lactones are crystalline substances which should prove valuable additions to our

[1] Read at the meeting of the American Chemical Society, Buffalo, N. Y., September, 1931; and also published in Ind. Eng. Chem. vol. 24, p. 375, 1932.
[2] Isbell and Frush, B. S. Jour. Research, vol. 6 (RP328), p. 1145, 1930.
[3] Nef, Ann., vol. 403, p. 322, 1914.

supply of organic acids. Many uses for these weak organic acids or their lactones will undoubtedly be found when they are more readily available.

As may be seen from the following equation, the new process for the electrolytic oxidation of the aldose sugars, which has been developed by the authors,[4] is superior to the older method of bromine oxidation because the reaction product does not contain any objectionable substances derived from the oxidant:

$$\underset{\text{Dextrose}}{2C_6H_{12}O_6} + \underset{\text{Catalyst}}{CaCO_3 + CaBr_2} + H_2O \xrightarrow[\text{Electrolysis}^5]{} \underset{}{Ca(C_6H_{11}O_7)_2} + CaBr_2 + CO_2 + H_2$$

The bromide solution on electrolysis gives free bromine at the anode and hydrogen at the cathode. The bromine thus freed reacts with the sugar to give gluconic and hydrobromic acids. The calcium carbonate reacts with the acids as fast as they are formed and thus maintains a nearly neutral solution (about pH 6.2) in which the bromine combines as fast as it is liberated. The bromide is continuously regenerated; hence a small amount of it acts catalytically to facilitate the oxidation of a large quantity of the sugar. The amount of oxidation produced by a given quantity of current is very close to the theoretical. This shows that the reaction proceeds smoothly without the production of objectionable degradation products. The sugar is converted into the calcium salt of the sugar acid, and the only by-products are hydrogen and carbon dioxide which escape from the solution as gases.

II. SEMICOMMERCIAL PREPARATION OF CALCIUM GLUCONATE[6]

The adaptation of the electrolytic method for the production of calcium gluconate to a semicommercial scale was accompanied by very little difficulty such as is usually experienced in extending a laboratory method to a larger scale. This is due to the following facts: The process is unusually free from side reactions, the method does not necessitate careful control and can be applied efficiently under considerable variation of conditions, and the equipment is simple and easily constructed. The apparatus used in these studies is illustrated in Figure 1.

The outer jar is an ordinary 5-gallon water cooler. The solution is stirred with the mechanical stirrer shown in the center. There are four anodes and four cathodes, which are graphite rods 12 inches long and 1 inch in diameter. The cell was run at 10 amperes on an e. m. f. of 6 volts, and the temperature under these conditions was 55° C. On continuous operation at 20 amperes the temperature rose to 65° C. Although the cell ran satisfactorily at the higher rate it was usually run at 10 amperes; the current density was about 1.7 amperes per square decimeter of anode surface.

The cell was charged with 15 liters of water containing 2.7 kg of crystalline anhydrous dextrose, 0.75 kg of calcium carbonate, and 375 g

[4] See footnote 2, p. 571.

[5] The oxidation of two molecules of dextrose requires four Faradays of electricity.

[6] An application filed by one of the authors (H. S. I.) for a public-service patent covering this process has been placed in interference with applications filed by other parties. Those desiring to use the process are advised to await the outcome of the interference proceedings.

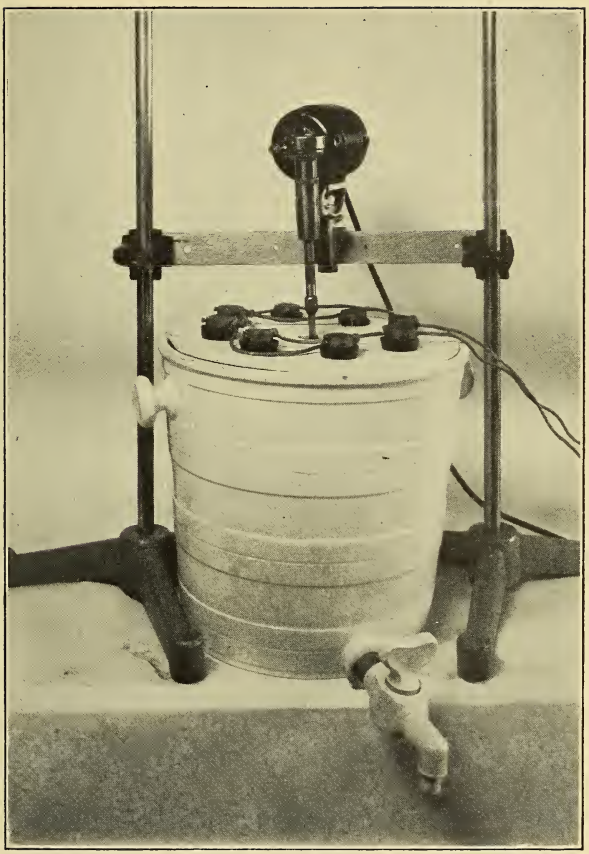

FIGURE 1.—*Electrolytic oxidation cell*

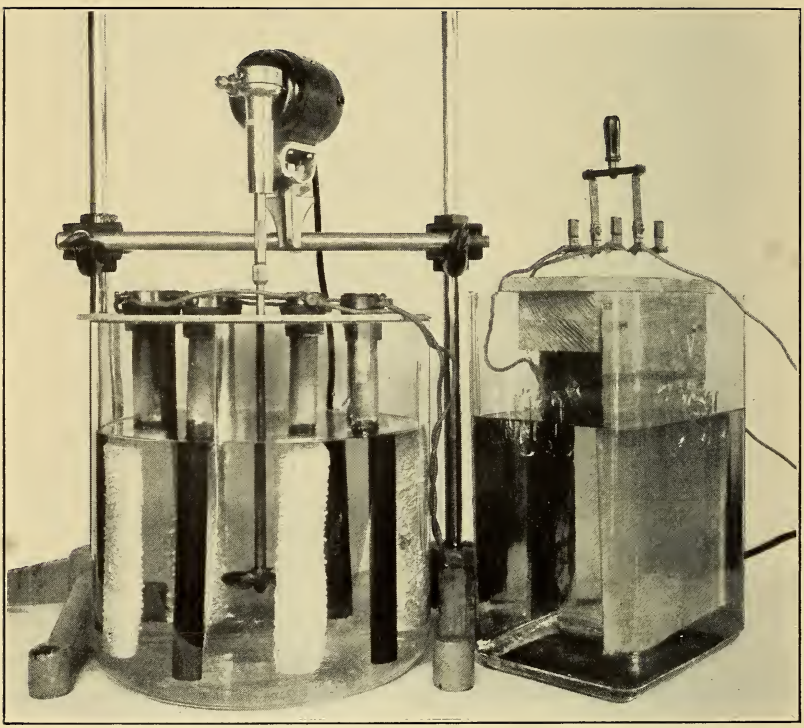

FIGURE 2.—*Cell showing calcareous deposit on cathodes*

of bromine.[7] The bromine reacts with the sugar and calcium carbonate to give calcium bromide and calcium gluconate. After oxidation had proceeded for three days at 10 amperes, considerable calcium gluconate crystallized from the electrolyte. A 5-liter portion was withdrawn and the calcium gluconate separated by filtration. The mother liquor and wash water were returned to the cell, together with 806 g of dextrose and 225 g of calcium carbonate. The oxidation was continued for 30 days with daily withdrawal of calcium gluconate and addition of dextrose and calcium carbonate in the amounts mentioned above. Each day's crop of calcium gluconate was recrystallized; the mother liquors from this recrystallization were used to wash the crude product obtained the following day, and were ultimately returned to the cell. A small amount of calcium carbonate reclaimed in the recrystallization was likewise returned. The volume of the electrolyte was kept at 15 liters, and occasionally the wash waters were concentrated in order to maintain this volume. At the end of the 30-day run, the entire electrolyte was filtered, and a sugar determination made upon the filtrate showed that 1.88 kg of sugar remained. The electrolyte was then returned to the cell, the required calcium carbonate added, and the amount of electricity (560 ampere hours) theoretically necessary to complete the oxidation of the remaining sugar was passed through. The calcium gluconate which crystallized was separated, and an additional yield was obtained on concentrating the mother liquors. After one recrystallization, these crops were combined with the previously recrystallized salt to give a total of 27.63 kg.

A quantity of calcium gluconate remained in the mother liquors and would not crystallize from the solution containing calcium bromide. This was reclaimed in part through precipitation as a basic calcium gluconate [8] by adding 1.5 kg of hydrated lime and heating to 70°. The basic salt was washed with lime water and then converted into the normal salt by removing the excess lime with carbon dioxide. The normal salt thus obtained after one recrystallization weighed 2.21 kg. The total yield of nearly pure calcium gluconate was 29.84 kg, or about 85 per cent of the theoretical.

At the end of the run the electrolyte was light colored and still in condition for continuing the process. In commercial operation it would be necessary to renew the elctrolyte occasionally. The frequency of renewal would depend upon the impurities in the raw materials and upon the operating conditions. Recovery of the bromide from the mother liquors will be discussed in Section IV.

As previously shown, under favorable conditions the sugar is nearly quantitatively oxidized. The experimental conditions in this case were not ideal, and there were relatively larger losses in handling and recrystallizing the material and in overoxidation than would occur in actual plant operation. Excess calcium gluconate caused the electrolyte to become thick enough to prevent thorough stirring, and some local overoxidation resulted. This difficulty would be overcome in a plant through continuous removal of the calcium

[7] The bromine reclaimed by one of the methods suggested in Section IV of this paper may be used. If the method yielding free bromine is employed, the bromine may be collected directly in the sugar solution. The resulting solution contains practically no free bromine, and hence is easily handled.

[8] The crude basic calcium gluconate obtained from the impure electrolyte after a washing with lime water may be used in a subsequent run in place of some of the calcium carbonate. The calcium gluconate is then recovered along with the crude oxidation product. However, in the event that the basic salt is very impure, it is probably better to prepare the normal salt by decomposition with carbon dioxide in the usual manner.

gluconate by a suitable filter. After one recrystallization the product usually contains a small quantity of calcium bromide. Although calcium gluconate is easily recrystallized from hot water, and calcium bromide is much more soluble than calcium gluconate, still the bulky nature of the calcium gluconate makes the removal of the last traces of the bromide difficult. This is the most troublesome step in the process, but with proper facilities for crystallizing and washing the salt in large quantity, it would be less burdensome.

In larger units, cooling coils would be necessary. In the experiments reported in this paper, no cooling device was used, but cooling is necessary when the described cell is run at its maximum capacity.

A small amount of foaming occurs during the reaction, but this does not cause any trouble provided the cell is not too full. The foaming may be reduced by the addition of a few drops of an antifoam compound, such as caprylic alcohol, although this is not necessary.

Costs for the production of calcium gluconate by this process depend largely upon the volume of production. Reliable figures can not be determined from the operation of a unit of the size outlined in this paper, but some idea of their magnitude may be obtained. A comparatively small initial investment is necessary as the equipment is simple and easily constructed. As shown in Table 1, the cost of the raw materials may be conservatively estimated at about $6 per 100 pounds. This estimate is based on current prices and the results obtained in the experimental run. The cost for electricity will depend largely on the location and operating conditions. The cell used in the run under discussion requires about 6 volts for a current of 10 amperes, and produces about 2 pounds of calcium gluconate per day; if the capacity is doubled by increasing the voltage to 12 volts, more energy is lost as heat. The most economical operating conditions, as well as the cost for electrodes, maintenance, operation, depreciation, etc., can not be determined at this time, but it is evident that calcium gluconate may be made by the new process at a very reasonable figure.

TABLE 1.—*Semicommercial manufacture of calcium gluconate*

	Chemicals actually used in experimental run		Chemicals required to produce 100 pounds of calcium gluconate.
	Pounds	*kg*	*Pounds*
Dextrose	59.3	26.9	90 at $0.05 = $4.50
Calcium carbonate	16.1	7.3	25 at .01 = .25
Bromine	.83	.375	1.25 at .36 = .45
Electricity (for electrolysis only)	51 kw.-hr.		80 kw.-hr. at .01 = .80

Estimated cost of above items, $6.

Experimental run gave 29.84 kg (65.78 pounds) of calcium gluconate, $Ca(C_6H_{11}O_7)_2.2H_2O$ which is about 85 per cent of the theoretical yield.

III. POLARIZATION AND CRACKING OF THE ELECTRODES

In the course of the electrolytic oxidation the cathodes occasionally become coated with a calcareous deposit. The composition of this deposit varies considerably, but it always contains calcium carbonate, calcium hydroxide, calcium gluconate, and a small amount of material which reduces Fehling's solution. The coating is gen-

erally formed when dilute solutions are employed and is seldom found when the electrolyte contains considerable sugar or calcium gluconate. Presumably the sugar derivatives, by their solvent action, prevent the deposit of calcium hydroxide in the alkaline region immediately surrounding the cathode.

A typical cathode coating obtained with a dilute solution is illustrated in Figure 2. We have found that this deposit may be removed by reversing the current. The previously coated cathode then becomes the anode, and the hydrobromic acid formed in its vicinity quickly dissolves the deposit.

A number of experiments were made to determine the effect of reversing the direction of current upon the efficiency of the oxidation. The determinations were made on solutions containing 45 g of dextrose, 8 g of calcium bromide, and 25 g of calcium carbonate in 1 liter of water. The solution was electrolyzed in a flask fitted with graphite electrodes and a mechanical stirrer. A timing device was included in the circuit so that the direction of the current could be reversed at definite intervals. As shown in Table 2, reversing the current lowered the efficiency. With an alternating 60-cycle current, practically no oxidation occurred.

TABLE 2.—*Effect of reversing the direction of the current on the current efficiency*

Time (in minutes) between changes in the direction of the current	Current density	Current efficiency [1]
	Amperes/dm [2]	
1	1.6	39.4
1	3.2	53.5
25	1.6	80.1
400 (approx.) [2]	1.6	95.5
∞ [3]	1.6	94.7

[1] Current efficiency is the percentage of the sample found to have been oxidized after 13.4 ampere-hours. The quantity of electricity theoretically required for complete oxidation of the sample is 13.4 ampere-hours.
[2] The current was reversed whenever it was believed necessary to prevent the formation of a heavy deposit.
[3] The current was not reversed and consequently considerable deposit formed on the cathode.

It is apparent from the results given in Table 2 that the current should not be reversed except when it is necessary to clean the electrodes. If the proper conditions are maintained this is seldom required. In the continuous oxidation reported, the current was reversed three or four times at the beginning of the run.

Frequently, with concentrated solutions and high-current densities the anodes split longitudinally, but the cathodes are unaffected. The effect seems to be mechanical for the graphite is not corroded. The cracks usually are filled with crystalline material, and the difficulty occurs only during long continued oxidation. This suggests the explanation that the electrodes originally contained minute cracks in which calcium gluconate or some other substance collected, producing fractures in a manner analogous to the fracture of rocks by the freezing of water. This difficulty may be largely overcome by impregnating the electrodes with paraffin to fill up the minute cracks and thus prevent penetration by the electrolyte.

IV. RECOVERY OF THE BROMIDE

In a plant it would be necessary to recover the bromide from mother liquors which become contaminated by long-continued use. The simplest method consists in evaporating the residues to dryness and igniting to remove the organic matter. The ash which remains is largely calcium carbonate, oxide, and bromide, and hence it may be used in a subsequent electrolytic oxidation as a source of bromide. Frequently it contains objectionable impurities, in which case it requires further purification. The ash or residue may be extracted with water and the aqueous solution used directly; or the bromine may be liberated by electrolysis of the extract after acidification with sulphuric acid. In the latter case the free bromine is distilled into a dextrose solution containing calcium carbonate in suspension.

In the semicommercial experiment described in a previous section, the residues were ignited and the ash extracted with 2 liters of boiling water. The extract was acidified with sulphuric acid, and the bromine liberated by electrolysis. Platinum electrodes were used. Air was bubbled through the solution to aid in removing the bromine and the vapors were led into a solution containing 2.7 kg of dextrose, and 750 g of calcium carbonate in suspension. After all the bromine had been collected in the sugar solution it was transferred to the cell and used directly for the preparation of more calcium gluconate in manner analogous to that described above. The bromine recovered (and determined by bromide analysis upon the fresh electrolyte) was about 53 per cent of that originally used. This figure is not indicative of the efficiency of the method of recovery because of preventable losses in handling, and retention of the bromide in the calcium gluconate. In this connection it should be recalled that the cost of the bromine is only a small fraction of the total cost.

V. BASIC CALCIUM GLUCONATE

Although Fischer[9] reported in 1890 that gluconic acid forms a basic calcium salt, the compound has not been studied further nor its composition determined. The writers have found that the difficultly soluble basic salt obtained from calcium gluconate by the addition of hydrated lime may be used to advantage for the separation of calcium gluconate from impure solutions which will not yield the crystalline normal salt. As stated in a previous paragraph, it was used for this purpose in reclaiming calcium gluconate from the residual mother liquors. The product obtained was impure and contained an excess of lime. It is not necessary to prepare the pure salt when it is to be used for separating calcium gluconate, since the excess lime is removed later as the carbonate. However, in order to determine the composition of the substance it is necessary to obtain it pure. This may be accomplished by taking advantage of the fact that basic salts of this type are less soluble in hot water than in cold. The following procedure was used for preparing the basic salt of gluconic acid. To a solution of 100 g of pure calcium gluconate in 1,400 ml of water was added 600 ml of milk of lime prepared from 27 g of CaO. Both solutions were kept ice cold. The resulting mixture was filtered quickly on a large Büchner funnel with a coarse filter paper. After

[9] Fischer, Ber., vol. 23, p. 2615, 1890.

the addition of a small quantity of decolorizing carbon the solution was filtered again. The basic salt was precipitated by warming the clear filtrate on the steam bath. It was separated by filtration while hot, washed thoroughly with hot lime water, and finally with a small quantity of hot water, then dried to constant weight at 80° in vacuo (about 24 hours).

During its preparation it was protected as much as possible from the carbon dioxide of the air, and when dried was kept in small air-tight bottles until used. The crude basic calcium gluconate may be prepared with good yield, but the quantity of the pure salt obtainable by the above procedure varies considerably with the technique. As much as 40 g of the pure dry salt has been obtained, but in case the solution of calcium gluconate and the milk of lime are not cold, or an excess of lime is added, the basic salt may precipitate before the mixture can be filtered, and the yield from the filtrate is then very small.

Several preparations by the above procedure, dried to constant weight in vacuo at 80° C., gave consistent analyses, corresponding to the formula $Ca(C_6H_{11}O_7)_2.2CaO$. However, when dried at lower temperatures the salt appears to hold varying amounts of water. The calcium-oxide content usually ran a little low and the carbon somewhat high; this is probably caused by the absorption of a small amount of carbon dioxide during the preparation of the sample.

Analyses calculated for $Ca(C_6H_{11}O_7)_2.2CaO$: C, 26.55; H, 4.09; Ca, 22.16; CaO, 20.68. *Found:* C, 27.09, 27.09; H, 4.03, 4.07; Ca, 22.10; CaO, 20.30.

Washington, March 9, 1932.